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# Long-term follow-up of cortical hyperexcitability in Japanese Unverricht-Lundborg disease.

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## Abstract

*Purpose:* To delineate chronological changes of cortical hyperexcitability by long-term follow-up of the amplitudes of somatosensory evoked potentials (SEPs) in patients with Japanese Unverricht-Lundborg disease (ULD).

*Methods:* SEPs to median nerve stimulation were repeatedly examined in 7 genetically diagnosed ULD patients with the mean interval of 11.9 years. The degree of temporal changes in the amplitude of 3 early cortical components, N20, P25 and N35, to the age was analyzed and compared with that of healthy subjects.

*Results:* Their clinical course was almost stable during the follow-up period, namely cessation of generalised tonic-clonic seizures and little or no progression of myoclonus. SEP amplitudes of P25 and N35 were enlarged in all patients and were gradually decreased with aging in ULD on average. The degree of temporal changes of P25 and N35 in ULD was similar or even lower than that of healthy subjects.

*Conclusions:* Enlarged but relatively stable SEP amplitudes had a consistency with so-called self-limited clinical course in Japanese ULD. SEP amplitude could be one of the surrogate markers of the degree of cortical hyperexcitability in ULD during the long-term follow-up period.

## Key Words

Unverricht-Lundborg disease; somatosensory evoked potential; giant SEP

## Abbreviations

ULD, Unverricht-Lundborg disease; EPM1, progressive myoclonus epilepsy type 1; SEP,

somatosensory evoked potential; GTCS, generalised tonic clonic seizure

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## 1. Introduction

Unverricht-Lundborg disease (ULD) is one of progressive myoclonus epilepsies that is characterized by myoclonus, epileptic seizures and cerebellar ataxia, and nowadays is called progressive myoclonus epilepsy type 1 (EPM1)<sup>1)</sup>. In ULD patients, the somatosensory evoked potentials (SEPs) usually show enhanced cortical components after N20 (i.e., giants SEPs) as a marker of cortical hyperexcitability to the external stimuli<sup>2),3)</sup>. Although the term “progressive” was assigned, it was reported that the European ULD patients showed self-limited progression in the later life<sup>4)</sup>. By investigating neurophysiological correlates of this clinical course, we just recently reported 2 Japanese ULD patients who showed clinically no or little progressive course. Their bimodal waveforms of N35 in the previous SEPs became unimodal over the course of 16 years, and it suggests decreased cortico-cortical connectivity and/or cortical excitability<sup>5)</sup>. We also reported the amplitudes of the early SEP components (N20, P25 and N35) were almost stable, although these components were already enlarged in the previous SEP. However, it is not certain whether waveform change of N35 is common or not because we studied only 2 patients. We could not evaluate the chronological changes in amplitudes of each cortical SEP component, either. Herewith we extensively evaluated 5 more genetically proven ULD patients.

In this report, we further described the temporal changes in SEP amplitudes of a total of 7 Japanese ULD patients to delineate the chronological changes of responsive, cortical hyperexcitability. Only abstract is available for this study<sup>6)</sup>.

## 2. Patients and methods

We recruited 7 Japanese patients with genetically diagnosed ULD (4 men and 3 women; mean age at the first SEP examination of 27.6 years, ranged from 17 to 42 years). During the follow-up period, we collected the changes in the frequency of generalised tonic clonic seizures (GTCSs), and the degree of myoclonus for each patient by using the simplified myoclonus rating scale as follows<sup>4)</sup>, 0 = no myoclonus; 1 = minor myoclonus, no interference with daily living; 2 = mild myoclonus, interference with fine movements and/or speech, no interference with walking; 3 = moderate myoclonus, patient still able to walk without support; 4 = moderate to severe myoclonus, patient able to stand, unable to walk without support; 5 = severe myoclonus, patient wheelchair-bound or bedridden.

The SEPs were not recorded with completely the same equipment and condition, since the patients belonged to several institutes and the repeated examination were done with the mean interval of 11.9 years (ranged from 4 to 16 years). Recording conditions were quite consistent at least within each patient. Furthermore, as compared with previous study<sup>5)</sup>, the overall recording condition was essentially consistent except for stimulus frequency in several patients as follows. The median nerve was stimulated at the wrist at a fixed rate of 1.1-3.0 Hz (1.1 Hz in 3 patients and 2.0 Hz in 4 for the previous recording; 1.1 Hz in 5 and 3.0 in 2 for the present recording) and the stimulus intensity was adjusted to produce a clear twitch of the thenar muscle. Short latency SEPs were recorded from C3/C4 according to the International 10-20 System or CP3/CP4 by 10-10 System of the American

EEG Society. The electrode impedance was kept below 5k $\Omega$ . The ipsilateral earlobe to the stimulated hand (A1 or A2) or the linked earlobes (A1 + A2) were used as the reference. The bandpass filter was within the range of 0.5-3000 Hz. At least 200 responses were averaged.

We adopted 3 components of N20, P25 and N35. Amplitudes of P25 and N35 were measured from the preceding opposite peak and those of N20 were measured from the baseline. An SEP was judged as “giant” when P25 was more than 6.3  $\mu$ V or N35 was more than 9.8  $\mu$ V<sup>7)</sup>. We also compared the amplitudes of the 3 components of ULD patients in the previous and present states with those of healthy subjects (N=19; 11 men and 8 women; mean age at the SEP examination of 49 years, ranged from 22 to 74 years) by Mann-Whitney U test. A tangential component of N30-P30 was not adopted in this study, since we could not detect the reliable N30-P30 from shortage of the number of the recorded electrodes.

In order to evaluate the chronological changes in SEP amplitude in ULD, we compared the early cortical components of SEPs between previous and present states by Wilcoxon signed-rank test. In addition, we analyzed the relationship between the age at SEP recording and its amplitudes. Namely we calculated the averaged value of the ages and amplitudes of 7 patients both at previous and present SEP recording, and then extrapolated the chronological changes. Since SEP amplitude increased with aging even in healthy subjects<sup>8),9)</sup>, we compared the gradient of ULD patients with those of 19 healthy subjects as reported previously<sup>9)</sup>.



### 3. Results

As for the clinical symptoms, all the patients showed a cessation of GTCs and a stable or little worsened myoclonus. The medications at the previous and present SEP recording are shown in Table 1. During the follow-up period, the dosage of the medications did not show clear tendency. Namely, medication was increased in 4 patients (Patient 3, 4, 5, and 6) whereas it was decreased in 3 patients (Patient 1, 2, and 7). The averaged simplified myoclonus rating scale of 7 patients indicated almost stable but moderately severe, 3.4 and 3.9 at the previous and present recording, respectively.

In the previous recording, N20, P25 and N35 amplitudes (mean  $\pm$  S.D.) in 7 ULD patients were  $0.9 \pm 0.9 \mu\text{V}$ ,  $10.5 \pm 6.4 \mu\text{V}$  and  $12.9 \pm 7.0 \mu\text{V}$ , and those in the present evaluation were  $2.3 \pm 1.6 \mu\text{V}$ ,  $9.9 \pm 6.1 \mu\text{V}$  and  $10.8 \pm 4.0 \mu\text{V}$ , respectively (Table 2). Both in the previous and present recording, the amplitudes of N20 in ULD were lower than those of healthy subjects ( $p < 0.05$ ). On the other hand, the amplitudes of P25 and N35 in ULD were higher than those of healthy subjects and only N35 amplitudes reached statistical significance ( $p < 0.05$ ). All 7 patients fulfilled the criteria of the giant SEPs at least once during their clinical course.

The amplitudes of P25 and N35 in some of the ULD patients tended to increase during the follow-up period, but no significant difference in amplitude was found between previous and present data by Wilcoxon signed-rank test. Whereas, only 1 patient (Patient 5) showed relatively drastic decrease in SEP amplitude for P25 and N35 (Fig. 1(b), (c)). In total, the gradients of temporal

changes of N20, P25 and N35 amplitudes for age in the 7 ULD patients were 0.119, -0.051, and -0.178, respectively. As compared with healthy subjects (N20: 0.048, P25: 0.139, N35: 0.089), that of P25 and N35, were even lower than those of healthy subjects (Fig. 1). Namely, enhanced amplitude of P25 and N35 reflects the responsive, cortical hyperexcitability across all the 7 patients, but the degree of its gradient in temporal change for aging is not increased at all. When 1 patient (Patient 5) was excluded because she showed dramatically decrease in amplitudes, the gradients of temporal changes of N20, P25 and N35 amplitudes for age in the 6 ULD patients were quite similar to those of aging in healthy subjects, i.e., 0.141, 0.156, and 0.073, respectively (not shown in the figure).

The waveform change of N35 from bimodal to unimodal over the course was observed only in 2 out of 7 patients, both of whom we reported in the previous report<sup>5)</sup>.

#### 4. Discussion

We demonstrated that SEP amplitudes were enlarged or giant in genetically diagnosed ULD patients throughout the follow-up period, that was quite consistent with previous reports.

We also showed that once enlarged SEP amplitude of P25 and N35 gradually decreased on average with aging in ULD. Indeed, 5 patients for P25 and 4 patients for N35 demonstrated that enlarged SEP amplitude gradually increased with aging, but the degree of increment was quite comparable to that of aging in healthy subjects (Fig. 1). Namely, most likely we were able to demonstrate that responsive cortical hyperexcitability was not progressive for aging but relatively stable in the primary sensori-motor cortices in Japanese ULD. These electrophysiological findings in quite parallel with clinical course in our patients were quite consistent with self-limited clinical course as reported previously<sup>4)</sup>. Therefore, SEP amplitude could be one of the surrogate markers of the degree of cortical excitability and at least a part of pathophysiology in ULD during the long-term follow-up period. However, It is unclear that self-limited progression was observed in all Japanese ULD patients, since one of the patients (Patient 5), who showed a little worsened myoclonus, showed relatively drastic decrease in SEP amplitude. It might be explained by the paradoxical association between giant SEP and the degree of myoclonus, which was clearly reported in patients with cortical myoclonus previously<sup>10)</sup>.

In addition, some ULD patients in other reports with genetically diagnosed show continuous progression in terms of clinical symptoms as well as electrophysiological results<sup>11)</sup>. In our previous

report we mentioned the waveform change of N35 from bimodal to unimodal could reflect a lesser degree of cortico-cortical connectivity and/or decreased cortical hyperexcitability in ULD patients. The additionally recruited 5 patients did not show similar waveform change of N35 component, which suggests not only this waveform change but also chronological changes in SEP amplitudes contribute to self-limited progression.

Further case accumulation showing variable clinical course is indispensable to further clarify the clinico-electrophysiological correlates and to solve these clinical questions in patients with ULD. The current long-term observation in this study started mostly after age 20 years in 6 out of 7 patients, but it was done until before 50 years in 6 out of 7 patients. Therefore, it may not be completely excluded that ULD patients in much older age more than 50 years are actually so stable. Thus, it is important to continue the evaluation of our patients to see if changes in SEP can manifest in older patients.

There are several limitations in this study. Firstly, the change of SEP amplitude over a decade might be due to chronic exposure to antiepileptic or antimyoclonic drugs. In general, most antiepileptic drugs seem to decrease the SEP amplitude<sup>12)</sup>. The dosages of these drugs were not completely the same during the follow-up period as well. Secondly, as mentioned in Methods, the recording conditions were not completely the same among studied patients and within each patient. However, except stimulus rate, we consider that the influence of the different recording conditions on the SEP amplitude was quite small. With regard to the stimulus rate, in the previous reports, the

amplitude of P25 decreased and N35 was not significantly altered once the stimulus rate gradually increased from 1.0 to 5.0 Hz<sup>13),14)</sup>. In our study, the stimulus rate increased from 2.0 Hz to 3.0 Hz in 2 patients (Patient 5 and 6), and that decreased from 2.0 Hz to 1.1 Hz in the other 2 patients (Patient 3 and 4) between previous and present recordings. The change of amplitude, such as decreased amplitude of P25 only in Patient 5, might be partly influenced by the change of stimulus rate. Despite these limitations, our study has some value in evaluating long-term clinico-electrophysiological changes in Japanese ULD.

## 5. Conclusions

We demonstrated that SEP amplitudes were enlarged or giant in genetically diagnosed ULD patients throughout the follow-up period. We also showed that once enlarged SEP amplitude of P25 and N35 gradually decreased with aging in ULD. Enlarged but relatively stable or gradually decreased SEP amplitudes had a consistency with so-called self-limited clinical course in ULD. SEP amplitude could be one of the surrogate markers of the degree of cortical hyperexcitability in ULD during long-term follow-up period.

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## Disclosure of Conflicts of Interest

None of the authors has any conflict of interest to disclose.

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## Figure Legends

Figure 1. Correlation between the age at SEP recording and its amplitudes in 7 ULD patients. Values of N20 (A), P25 (B) and N35 (C) (different colored lines) and the gradients of their temporal changes drawn by calculating the averaged value of the ages and amplitudes between previous and present SEP recordings (black lines) in 7 patients are compared with linear regression curves of 19 healthy subjects (gray lines).

N20 amplitudes were much smaller and P25 and N35 amplitudes larger in ULD patients. As for the components associated with giant SEP (i.e., P25 and N35), 7 ULD patients showed a tendency of slight decrease in amplitude during the follow-up period, and the degree of its tendency was even lower than that of healthy subjects.

## Highlights

- 1) We followed SEP amplitudes in 7 Japanese Unverricht-Lundborg disease (ULD) patients.
- 2) Clinical course of all patients was almost stable during the follow-up period.
- 3) The SEP amplitudes were enlarged but relatively stable over 10 years.
- 4) SEP amplitudes had a consistency with so-called self-limited clinical course in ULD.
- 5) SEP amplitudes can be a biomarker of the degree of cortical hyperexcitability in ULD.

Figure 1.

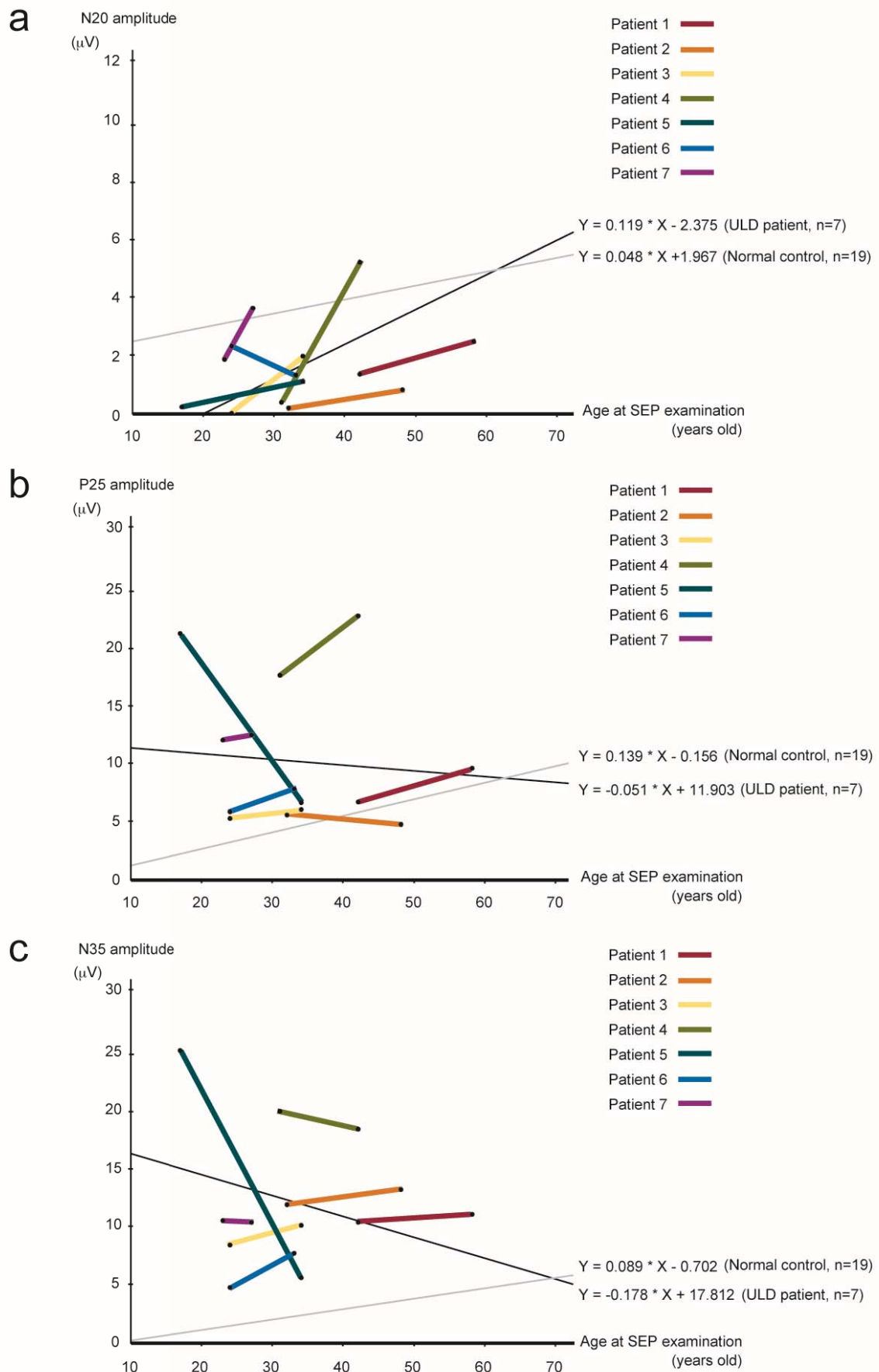


Table 1

Medications at the previous and present SEP recording in 7 patients (mg/day).

| Previous  |            |  | Present |  |  |
|-----------|------------|--|---------|--|--|
|           | Age at SEP |  |         | Age at SEP   |  |
| Patient 1 | 42         | VPA 1,400, CZP 4.5, PB 120, Piracetam 15,000 | 58      | VPA 700, CZP 6, PB 60, Piracetam 6,000             |  |
| Patient 2 | 32         | VPA 3,600, CZP 12, PHT 300, CBZ 400          | 48      | VPA 2,000, CZP 8, ZNS 300, DZP 5                   |  |
| Patient 3 | 24         | VPA 1,100, CZP 6, ZNS 200                    | 34      | VPA 1,800, CZP 6, ZNS 200, Piracetam 33,000        |  |
| Patient 4 | 31         | VPA 1,200, PB 90, ZNS 200                    | 42      | VPA 1,200, CZP 6, PB 60, ZNS 200, Piracetam 27,000 |  |
| Patient 5 | 17         | VPA 1,200, CZP 1.3, PB 40, PRM 400           | 34      | VPA 1,800, CZP 4, ZNS 600, PRM 300, AZM 250        |  |
| Patient 6 | 24         | VPA 800, CBZ 200                             | 33      | VPA 1,400, PB 50, ZNS 200                          |  |
| Patient 7 | 23         | VPA 800, CZP 2, Piracetam 12,000             | 27      | VPA 600, CZP 2, Piracetam 12,000                   |  |

VPA: valproic acid, CZP: clonazepam, PB: phenobarbital, PHT: phenytoin, CBZ: carbamazepine, ZNS: zonisamide, DZP: diazepam, PRM: primidone, AZM: acetazolamide

Table 2  
 Latency and amplitude of cortical components of SEPs in 7 patients, latency (ms) / amplitude (μV).

| Previous       |            |                        |                         |                         | Present |            |                        |                        |                         |
|----------------|------------|------------------------|-------------------------|-------------------------|---------|------------|------------------------|------------------------|-------------------------|
|                | Age at SEP | N20                    | P25                     | N35                     |         | Age at SEP | N20                    | P25                    | N35                     |
| Patient 1      | 42         | 20.6 / 1.3             | 26.6 / 6.6*             | 30.9 / 10.3*            |         | 58         | 20.1 / 2.5             | 25.4 / 9.5*            | 30.8 / 10.9*            |
| Patient 2      | 32         | 19.2 / 0.2             | 24.8 / 5.5              | 31.5 / 11.8*            |         | 48         | 20.7 / 0.8             | 24.9 / 4.7             | 32.3 / 13.0*            |
| Patient 3      | 24         | 23.7 / 0.0             | 29.1 / 5.2              | 37.9 / 8.3              |         | 34         | 20.6 / 2.0             | 25.3 / 6.0             | 31.4 / 10.0*            |
| Patient 4      | 31         | 23.8 / 0.4             | 32.0 / 17.4*            | 38.7 / 19.7*            |         | 42         | 20.9 / 5.1             | 26.6 / 22.4*           | 33.1 / 18.2*            |
| Patient 5      | 17         | 20.0 / 0.2             | 26.0 / 21.0*            | 32.6 / 24.8*            |         | 34         | 20.3 / 1.1             | 25.8 / 6.6*            | 31.0 / 5.6              |
| Patient 6      | 24         | 20.4 / 2.3             | 26.6 / 5.8              | 34.9 / 4.7              |         | 33         | 20.5 / 1.3             | 27.4 / 7.8*            | 35.3 / 7.6              |
| Patient 7      | 23         | 14.2 / 1.8             | 20.2 / 11.9*            | 31.8 / 10.4*            |         | 27         | 18.5 / 3.6             | 24.0 / 12.3*           | 32.7 / 10.3*            |
| Average ± S.D. | 27.6       | 20.3 ± 3.2 / 0.9 ± 0.9 | 26.5 ± 3.6 / 10.5 ± 6.4 | 34.0 ± 3.2 / 12.9 ± 7.0 |         | 39.4       | 20.2 ± 0.8 / 2.3 ± 1.6 | 25.6 ± 1.1 / 9.9 ± 6.1 | 32.4 ± 1.5 / 10.8 ± 4.0 |

\* Giant SEP: P25 > 6.3 or N35 > 9.8 μV (Ikeda et al., 1995)